based dosing are needed to compare the glycemic benefit of this approach with the additional patient burden of carbohydrate counting.

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Decline in HbA1c during the first year on elexacaftor/tezacaftor/ivacaftor in the Danish cystic fibrosis population

B. Nielsen[1], M. Olsen[2], I. Mathiesen[1], T. Pressler[2], S. Jensen-Fangel[3], C. Ritz[4], T. Almdal[5], D. Faurholt-Jepsen[2]. *[1]Cystic Fibrosis Centre Copenhagen, Department of Infectious Diseases, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [2]Copenhagen Cystic Fibrosis Center, Rigshospitalet, Copenhagen, Denmark; [3]Department of Infectious Diseases, Aarhus University Hospital, Aarhus, Denmark; [4]National Institute of Public Health, University of Southern Denmark, Odense, Denmark; [5]Department of Endocrinology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark*

Background: In cystic fibrosis (CF), elexacaftor/tezacaftor/ivacaftor has a remarkable effect on lung function, but whether it affects glucose tolerance, including CF-related diabetes (CFRD) is not clear. We aimed to study both the effect of elexacaftor/tezacaftor/ivacaftor (ELX/TEZ/IVA) on glycosylated hemoglobin (HbA1c) in the Danish national CF population and changes in use of insulin in a CFRD subpopulation during the first year of treatment.

Methods: The entire Danish CF population is followed in either of two CF centers that measure HbA1c at baseline and 3, 6, 9 and 12 months after initiation of ELX/TEZ/IVA. All treated individuals aged 12 and older with a baseline sample and one or more follow-up samples were included in the study. During consultations with individuals with CFRD before and 12 months after initiation of treatment, information was obtain on use of insulin, hypoglycemic events, and if available, continuous glucose monitoring (CGM) from the past 30 days. Change in HbA1c 3 and 9 months after treatment initiation was assessed according to age group (12–25, 26–35, 36–45, 46–80), sex, glucose tolerance status (normal: <7.8 mM, impaired: 7.8–11.0 mM, CFRD: >11.0 mM 2-hour glucose), and previous modulator treatment (naïve, first-generation modulator) in mixed models using splines. The models included interaction between the concerned covariate and treatment time and were adjusted for the above-mentioned covariates. Changes in use of insulin and CGM parameters (covariance, average blood glucose, time below (<3.9 mM) and above (>10.0 mM) normal range) were assessed in paired Wilcoxon signed-rank tests.

Results: For 298 individuals with CF, average HbA1c was 43.3 mmol/mol at baseline, 1.9 mmol/mol (95% CI, −1.3 to −2.4 mmol/mol, $p < 0.001$) lower after 3 months of treatment, and 2.7 mmol/mol (95% CI, −2.2 to −3.1 mmol/mol, $p < 0.001$) lower after 9 months of treatment. In all age, sex, glucose tolerance, and previous treatment groups HbA1c had declined significantly after 3 months and even more after 9 months. The youngest individuals seemed to have the smallest decline in HbA1c (12–25 years: −1.8 mmol/mol, 95% CI, −0.7 to −3.0 mmol/mol, $p < 0.001$), whereas the decline was more pronounced in individuals aged 36 to 45 (−3.4 mmol/mol, 95% CI, −1.6 to −5.2 mmol/mol, $p < 0.001$) after 9 months. The decline was independent of glucose tolerance status (normal: −2.4 mmol/mol, 95% CI, −1.3 to −3.5 mmol/mol, $p < 0.001$; CFRD: −2.8 mmol/mol, 95% CI, −1.8 to −3.8 mmol/mol, $p < 0.001$) (Figure 1). In 26 individuals with CFRD, HbA1c declined, but we did not see a significant change in insulin use after 12 months (long-acting insulin: −2.0 international units (IE)/day, 95% CI, −5.0 to 3.5 IE/day, $p = 0.21$; short-acting insulin: −4.3 IE/day, 95% CI, −12.0 to 0.0 IE/day, $p = 0.05$). Neither the weekly number of hypoglycemic events (0.2, 95% CI, −3.2 to 1.8, $p = 0.81$) nor the CGM parameters (covariance, average blood glucose, time above and below range) changed.

Conclusions: In the Danish CF population, HbA1c continued to decline over 9 months of ELX/TEZ/IVA treatment regardless of age and diabetes status. In 26 individuals with CFRD, we were unable to detect a significant change in CFRD treatment or regulation. We speculate that factors other than insulin secretion (e.g., reduced inflammation, more physical activity) might contribute to the reduction HbA1c.

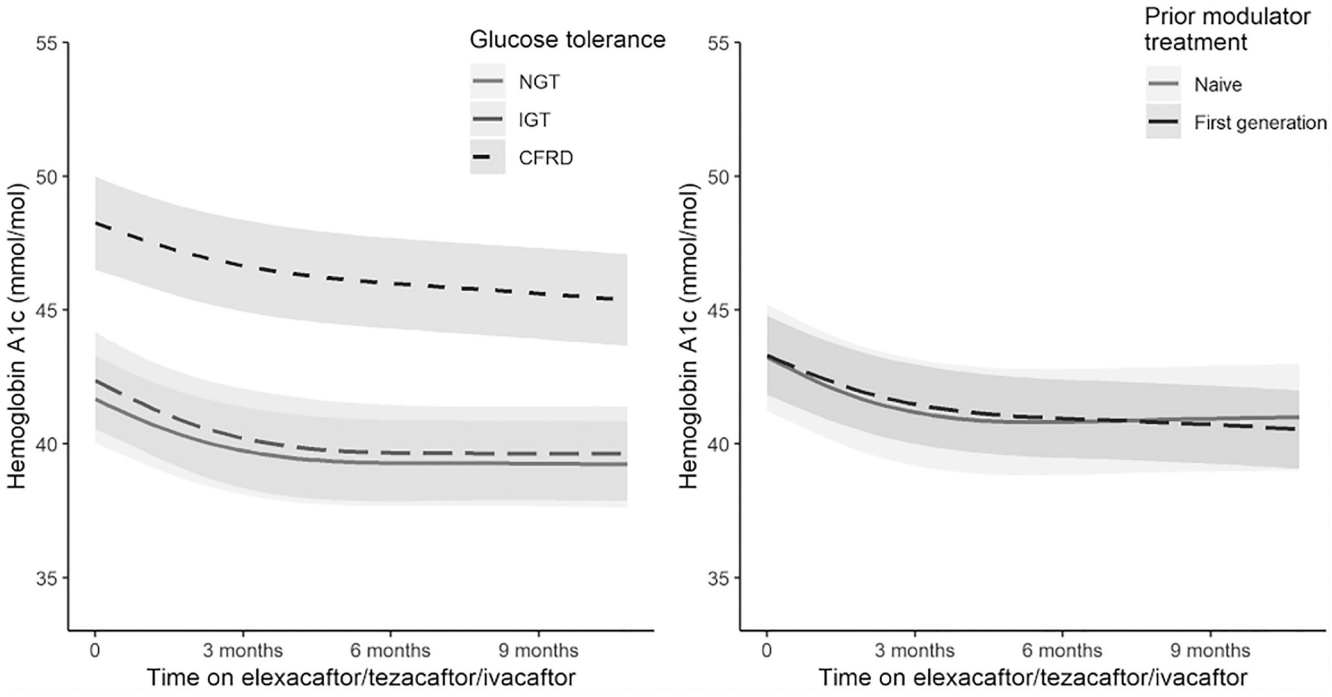

Figure 1 (abstract 6): Change in HbA1c according to glucose tolerance status and prior modulator treatment after initiation of ELX/TEZ/IVA treatment in 298 individuals with CF. Data were analyzed in mixed models with three knot splines. Covariates were fitted in interaction with treatment time and adjusted for age group, sex, glucose tolerance, and prior modulator treatment. NGT, normal glucose tolerance; IGT, impaired glucose tolerance; CFRD, cystic fibrosis–related diabetes; first generation, ivacaftor monotherapy, lumacaftor/ivacaftor, or tezacaftor/ivacaftor.